TSCA FIRST 10 DRAFT RISK EVALUATIONS
CANCER MOA

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
1-BP*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-1-bromopropane-1-bp"] Section 3.2.7.2 (page 158-159); Section 3.2.8.3 (page 163)	Evidence from chronic cancer bioassays in rats and mice suggests that 1-BP may pose a carcinogenic hazard to humans (IARC, 2018). Significant increases in the incidence of skin tumors (keratoacanthoma/squamous cell carcinomas) in male F344 rats, rare large intestine adenomas in female F344 rats, and alveolar/bronchiolar adenomas or carcinomas (combined) in female B6C3F1 mice were observed following exposure to 1-BP via whole-body inhalation for two years (NTP, 2011a). The exact mechanism/mode of action of 1-BP carcinogenesis is not established; however, an abundance of data exists and may provide a basis for weight of evidence considerations, including: in vitro tests, similarity in metabolism across species, SAR and other potential mechanisms of action. Although the results from Ames and other genotoxicity tests for 1-BP have been mixed, 1-BP was mutagenic in closed-system testing in the presence or absence of metabolic activation, induced DNA damage and repair in human cells in culture in the presence of metabolic activation, and induced mutations in mammalian cells in culture in the presence or absence of metabolic activation. Negative results were found for mutagenicity in inhalation studies in the Big Blue® mouse model (Weinberg, 2016; Young, 2016) but these studies do not provide clear evidence against a mutagenic mode of action of 1-BP carcinogenicity based on several conceptual, and methodological uncertainties (see Appendix I.5.6). Rodent metabolic studies have indicated 1-BP can be activated by CYP2E1 to at least five mutagenic metabolites/intermediates, including two

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		(glycidol and propylene oxide, see Appendix I.5.6; NTP (2013a), Jones and Walsh (1979), and IARC (2018)) that are clearly mutagenic and carcinogenic (IARC, 2000, 1994). Since humans have CYP2E1 activity in the lung and exhibit similar metabolic pathways for 1-BP as compared to rodents, the evidence from multiple species (rats and mice) for multiple cancer types following 1-BP exposure supports a carcinogenic hazard to humans. From the SAR point of view, 1-BP is a low molecular weight alkyl bromide with alkylating activity and two of its closest analogs (bromoethane and 1-bromobutane) both have provided positive Ames results when tested in closed systems. Bromoethane is a known carcinogen via the inhalation route of exposure, whereas 1-bromobutane has not been tested for carcinogenic activity. In addition to mutagenicity as a mechanism for induction of carcinogenicity by 1-BP, at least three other mechanisms, oxidative stress, immunosuppression, and cell proliferation, can act synergistically with mutagenicity and may thereby contribute to the multi-stage process of carcinogenesis.
Asbestos	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-asbestos-0"] **Ex. 5 Deliberative Process (DP)** Note: This is the link to the Scope Document; Draft RE not	**Ex. 5 Deliberative Process (DP)**

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
	yet released to the public and not yet gone to SACC peer review; draft available on RAD TSCA SP site	**Ex. 5 Deliberative Process (DP)**

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		Ex. 5 Deliberative Process (DP)

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		Ex. 5 Deliberative Process (DP)
MC*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-methylene-chloride-0"] Section 3.2.3.2.1 (page 245-247); Section 3.2.3.2.2 (page 247-258); Section 3.2.4.2 (page 264-266)	Mechanistic data show that methylene chloride has a mutagenic MOA involving DNA-reactive metabolites produced via a metabolic pathway catalyzed by GSTT1 (U.S. EPA, 2011). There are numerous genotoxicity tests showing positive results for methylene chloride, including assays for mutagenicity in bacteria and mutagenicity, DNA damage, and clastogenicity in mammalian tissues in vitro and in vivo (IARC, 2016; U.S. EPA, 2011). The most strongly positive results in mammalian tissues in vivo and in vitro were found in mouse lung and liver, tissues with the greatest rates of GST metabolism and the highest susceptibility to methylene chloride-induced tumors. To further strengthen the case for the role of GST-mediated metabolism, studies have demonstrated increases in damage with the addition of GSTT1 to the test system and decreases in damage by addition of a GSH depletory. The GSTT1 metabolic pathway has been measured in human tissues with activities that are lower than rodents. Thus, the cancer results in animal studies are relevant to humans, who do exhibit some GSTT1 activity (U.S. EPA, 2011). In particular, human cells have exhibited genotoxicity without exogenous addition of GSTT1 (U.S. EPA, 2011).

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		U.S. EPA (2011) evaluated sustained cell proliferation as an alternative MOA for methylene chloride-induced lung and liver cancer. Enhanced cell proliferation was not observed in the liver of female B6C3F1 mice exposed to 2000 ppm methylene chloride for up to 78 weeks (Foley et al., 1993) as cited in U.S. EPA (2011). Furthermore, acute and short-term inhalation studies showed enhanced cell proliferation in the lung; however, this effect was not sustained for longer exposure durations (83-93 days of exposure) (Casanova et al., 1996; Foster et al., 1992) as cited in U.S. EPA (2011). Based on these data, EPA doesn't expect sustained cell proliferation to be important, especially in the development of liver and lung tumors. Also, data were not identified suggesting a receptor-mediated mode (e.g., peroxisome proliferation resulting from PPAR-α activation; enzyme induction by CAR, PXR, or AhR activation). In accordance with U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, methylene chloride is considered "likely to be carcinogenic to humans" based on sufficient evidence in animals, limited supporting evidence in humans, and mechanistic data showing a mutagenic MOA relevant to humans. Therefore, this hazard was carried forward for dose-response analysis.
TCE	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-trichloroethylene-tce-0"] **Ex. 5 Deliberative Process (DP)**	**Ex. 5 Deliberative Process (DP)**

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		Ex. 5 Deliberative Process (DP)

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
PERC	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-perchloroethylene"] **Ex. 5 Deliberative Process (DP)** Note: This is the link to the Scope Document; Draft RE not yet released to the public and not yet gone to SACC peer review; draft available on RAD TSCA SP site	**Ex. 5 Deliberative Process (DP)**

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
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1,4-Dioxane*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-14-dioxane"] Section 4.2.3.2 (page 92-96); Section 4.2.4 (page 98-105); Section 4.2.4 (page 107-108)	Genetic Toxicity The genotoxicity of 1,4-dioxane has been tested in over 40 in vitro and in vivo studies. Briefly, 1,4-dioxane has been tested for genotoxic potential using various in vitro systems including prokaryotic organisms (S. typhimurium strains and E. coli strains), non-mammalian eukaryotic organisms, and mammalian cells, and in vivo systems using several strains of mice and rats. EPA previously evaluated these data in the IRIS assessment of 1,4-dioxane and concluded that 1,4- dioxane is either nongenotoxic or weakly genotoxic based on a weight-of-the-evidence analysis of the in vitro and in vivo genotoxicity studies (U.S. EPA, 2013c). EPA also concluded that 1,4- dioxane was not genotoxic in the majority of the available in vivo mammalian assays, although several studies have shown positive effects at or above doses of 1000 mg/kg/d. In this document, EPA conducted study evaluations using systematic review tools on select studies either as part of other endpoints, or independently for genotoxicity endpoints. EPA evaluated studies that were published after 2013 and had a confidence level of either high or medium quality. As shown in Table 4-4, two key publications were identified that met these criteria including two in vivo micronucleus assays that assessed the genotoxic potential of 1,4-dioxane in bone marrow and in liver (Itoh, 2019) and two in vivo mutagenicity assays (Itoh, 2019; Gi et al., 2018). Each of these studies is summarized below, followed by EPA's interpretation of how these studies add to the weight-of-

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		the-scientific evidence evaluation from the IRIS assessment on the potential for 1,4-dioxane to cause genotoxicity and/or mutagenicity. MOA conclusions The relationship between cell proliferation, hyperplasia, and 1,4-dioxane mediated tumor formation has not been established. Though several publications (Dourson et al., 2017; Dourson et al., 2014; McConnell, 2013) do provide evidence of cytoplasmic vacuolar degeneration and hepatocellular necrosis in rat and non-neoplastic lesions, the animal data does not support a dose response relationship between cell proliferation, hyperplasia, and liver tumors in rat and mouse studies. Kociba et al. (1974) reported hepatic degeneration and regenerative hyperplasia at or below dose levels that produced liver tumors, but incidence for these effects was not reported. Therefore, a dose-response relationship could not be evaluated, and the events cell proliferation and hyperplasia are not supported by available data. Finally, the doses in hepatotoxicity studies where cytotoxicity and cell proliferation were observed were greater than cancer bioassay dose levels. Integrating data across studies, dose-response relationships between cytotoxicity and tumor formation are not well established in the rat and mouse data and are inconsistent among bioassays and across exposure duration. EPA determined that evidence is not sufficient to support a MOA of cytotoxicity followed by sustained cell proliferation as a required precursor to tumor formation related to the metabolic saturation and accumulation of the parent compound, 1,4-dioxane (Dourson et al., 2017; Kociba et al., 1975). In addition, while genotoxicity is evident from high doses with in vitro and in vivo studies the occurrence at high doses and potential confounding with cytotoxicity does not support a mutagenic mode of action hypothesis at low doses in vivo. Other than liver tumors, no plausible MOA has been hypothesized for the other

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		tumor types associated with exposure to 1,4- dioxane. As a result, the proposed dose response approach for liver and other tumors is to show best fit of threshold and linear models applied to tumor data and linear default extrapolation in the absence of known MOA. Though the proposed cytotoxicity MOA is further considered through development of a threshold cancer model in Section 4.2.6 of this document, summary cancer risk calculations in Section 5.2 are based on a linear no-threshold model. Cancer Classification EPA re-evaluated the reasonably available evidence according to the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) previously summarized (U.S. EPA, 2013c). Evidence from human studies did not support or refute an association between occupational or general population exposure and increased risk of cancer, and by itself does not establish a clear causal relationship. 1,4-Dioxane exposure in animal studies leads to tumors in multiple tissues at multiple sites (Table 4-6) other than the initial points of contact (oral and inhalation) in males and females. There are data gaps for 1,4-dioxane inhalation and dermal exposure in humans and 1,4-dioxane dermal exposure in animals leading to carcinogenic effects. Human occupational studies examining the association between 1,4-dioxane exposure and increased cancer risk are inconclusive because they are limited by small cohort size and a small number of reported cancer cases. A large, high quality cohort study (Garcia et al., 2015) found no association between 1,4-dioxane and breast cancer rates. This study looked only at breast cancer and as such cannot be used to extrapolate to all cancers. Studies in multiple animal species show that chronic exposure to 1,4-dioxane induces tumors in multiple tissues by

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		both oral and inhalation exposure (Table 4-6). EPA classifies 1,4-dioxane as "likely to be carcinogenic to humans" based on animal evidence of carcinogenicity at multiple sites, in multiple species, and multiple routes of (U.S. EPA, 2013c). The National Toxicology Program classifies 1,4-dioxane as "reasonably anticipated to be a human carcinogen" (NTP, 2016) and NIOSH classifies it as a "potential occupational carcinogen"(ATSDR, 2012).
Carbon Tet*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-carbon-tetrachloride"] Section 3.2.4.2 (page 122-123); Section 3.2.4.3 (page 123-126); Section 3.2.4.3.2 (page 127)	The available data for carbon tetrachloride do not support a conclusion that this compound induces cancer though a mutagenic mode of action, however, there are important limitations to the database. While there is little direct evidence that carbon tetrachloride induces intragenic or point mutations in mammalian systems, studies have characterized formation of DNA adducts and chromosomal damage. Lipid peroxidation products (e.g., reactive aldehydes) may contribute to observed effects. The presence of cellular toxicity complicates the evaluation of the database and genetic damage has not been well studied at or below the doses at which tumors are observed. The EPA IRIS assessment of carbon tetrachloride classifies this compound as "likely to be carcinogenic to humans" based on sufficient evidence in animals by oral and inhalation exposure, i.e., hepatic tumors in multiple species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) in male and female mice exposed by oral and inhalation exposures (U.S. EPA, 2010). The systematic review did not identify additional genotoxicity studies with carbon tetrachloride with acceptable data quality based on the quality criteria in the Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a). This section summarizes available information on mode of action (MOA) for carbon tetrachloride carcinogenicity based on the MOA analysis performed in the 2010 EPA IRIS assessment (U.S. EPA, 2010) and additional information made available since 2010. The Guidelines for Carcinogen Risk Assessment

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		(U.S. EPA, 2005a) identifies steps for determining whether a hypothesized MOA is operative. The steps include an outline of the sequence of events leading to cancer, identification of the key events, and determination of whether there is a causal relationship between events and cancer. The EPA IRIS assessment reviewed MOA information for liver tumors and pheochromocytomas. IRIS described evidence in support of several potential mechanisms of action (described below) but concluded that "the overall MOA for carbon tetrachloride carcinogenicity across all levels of exposure is unknown at this time" (U.S. 3982 EPA, 2010). The IRIS assessment did not review information on potential MOAs for brain cancers and the MOA for brain cancer is also unknown. EPA has qualitatively evaluated the weight of evidence for several proposed MOAs for liver carcinogenicity using the framework outlined in EPA cancer risk guidelines (U.S. EPA, 2005a). This analysis considers the MOA analysis previously conducted by the IRIS program (U.S. EPA, 2010), more recent evidence, and information submitted to EPA through public comment (see Appendix K) to evaluate supporting and counterfactual evidence for proposed MOAs. A general correspondence has been observed between hepatocellular cytotoxicity and regenerative hyperplasia and the induction of liver tumors. At lower exposure levels, this correspondence is less consistent (U.S. EPA, 2010). A hypothesized carcinogenic MOA for carbon tetrachloride-induced liver tumors has been proposed and includes the following key events: (1) metabolism to the trichloromethyl radical by CYP2E1 and subsequent formation of the trichloromethyl peroxy radical, (2) radical-induced mechanisms leading to hepatocellular cytotoxicity, and (3) sustained regenerative and proliferative changes in the liver in response to

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		hepatotoxicity. This MOA appears to play a significant role at relatively high exposures, driving the steep increase in liver tumors in this exposure range. Data to characterize key events at low-exposure levels, however, are limited. Therefore, EPA also considered an alternate MOA that combines cytotoxic mechanisms at high doses with alternate, non-cytotoxic mechanisms as lower doses. Based on information in the IRIS assessment and public comments EPA-HQ-OPPT-2016-0733- 0066 and EPA-HQ-OPPT-2016-0733-0088, the following potential MOAs, including evidence for key events, are evaluated in Table 3-11 and Appendix K. • Liver cytotoxic MOA (Lipid peroxidation and cytotoxicity as proposed in comments submitted by ACC) • Combined MOA (non-cytotoxic at low dose and cytotoxic at high dose) Based on the qualitative MOA WOE for the alternative MOAs, there are significant data limitations to assess within certainty the causal considerations (i.e., biological plausibility, essentiality, dose-response concordance, consistency) for the postulated non-cytotoxic and 4023 cytotoxic key events that are expected to occur after carbon tetrachloride metabolism. The available data suggest that cytotoxicity is one major mechanism in the MOA of carcinogenesis at high exposures, however data also indicate that carbon tetrachloride can induce tumors in the absence of cytotoxicity, i.e., tumorigenesis in low dose female mice. There is limited information about mechanisms at lower doses.

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		EPA has reviewed the available literature and concludes that the MOA by which carbon tetrachloride induces pheochromocytomas in mice is unknown. Animal and in vitro evidence suggests that metabolism is an important contributor to the toxicity of carbon tetrachloride in the adrenal gland ((U.S. EPA, 2010) (see page 168)). Pheochromocytomas are relatively rare in people. Only a small number of chemicals have been associated with pheochromocytomas in mice, and there does not appear to be a common mechanism shared across these chemicals (U.S. EPA, 2010). Several potential MOAs for induction of pheochromocytomas in mice have been hypothesized but not experimentally supported, including endocrine disturbances, uncoupling of oxidative phosphorylation, disturbances in calcium homeostasis, impaired mitochondrial function, and hepatoxicity (Greim et al., 2009).
HBCD*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-cyclic-aliphatic-bromide-cluster-hbcd"] *No cancer risk estimate* Section 3.2.3.2 (page 302); Section 3.2.4.1.9 (page 308-309)	Genotoxicity A limited number of studies have investigated the genotoxicity of HBCD. Most standard Ames tests conducted with HBCD yielded negative results (Huntingdon Research Center, 1990; IBT Labs, 1990; Litton Bionetics, 1990; Pharmakologisches Institut, 1990; SRI International, 1990; Zeiger et al., 1987). Among the few assays performed to determine the genotoxicity of HBCD in eukaryotic systems, a reverse mutation assay in yeast (Litton Bionetics, 1990), one assay detecting chromosomal aberrations in human peripheral lymphocytes in vitro (Microbiological Associates, 1996a), and an in vivo mouse micronucleus test following intraperitoneal (i.p.) injections of HBCD (BASF, 2000) were negative, even when tested at cytotoxic concentrations. Some positive results have been reported in both bacteria (Ethyl Corporation, 1990b; IBT Labs, 1990) and mammalian cells (Helleday et al., 1999),(Ethyl Corporation, 1990a). It is noteworthy that in the mammalian cell study (Helleday et al., 1999), observed positive results for intragenic recombination were dose-

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		dependent, observed at nontoxic doses, and in two assays, specific for detecting mutations. However, the Ames tests in the same microbial strains that showed positive results (TA1535 and TA100) were negative in seven other studies, while he positive mutagenicity results observed in mammalian cells (Helleday et al., 1999) have not been confirmed by another group. There is also only limited evidence in the literature indicating that HBCD exposure may induce oxidative stress (An et al., 2013; Hu et al., 2009b). Carcinogenicity The carcinogenic potential of HBCD was not evaluated in any epidemiological studies. The only experimental animal study to examine cancer endpoints is an 18-month dietary study in mice that was only available as an incomplete report (Kurokawa et al., 1984). That study concluded that HBCD was not carcinogenic at dietary concentrations of 100, 1000 and 10,000 ppm. Overall, given the limited data, negative results in the majority of mutation assays and the negative results in two assays for chromosomal aberrations (BASF, 2000; Microbiological Associates, 1996a), there is indeterminate evidence to make a conclusion on the genotoxicity of HBCD. The only experimental animal study to examine cancer endpoints concluded that HBCD was not carcinogenic, however, this study was only available as an incomplete report (Kurokawa et al., 1984). Therefore, according to the U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is "inadequate information to assess the carcinogenic potential" of HBCD. As a result, this hazard was not carried forward for dose-response analysis.
PV 29*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-	The EPA concludes that C.I. Pigment Violet 29 presents a low hazard to human health across all routes of exposure (U.S. EPA, 2018b). This conclusion is based

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
	tsca/risk-evaluation-pigment-violet-29-anthra219-def6510"] *No cancer risk estimate* Section 4.2 (page 25-26)	on full study reports of the human health studies identified in the ECHA Database and Food Additive Petition (FAP) 8B4626 (ECHA, 2017; BASF, 1998). These full study reports concluded that no adverse effects were observed for all routes of exposure (oral, dermal, inhalation), nor were dermal or eye irritation effects reported. As a result, the EPA concludes that C.I. Pigment Violet 29 presents a low hazard to human health.
NMP*	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-n-methylpyrrolidone-nmp-0"] *No cancer risk estimate* Section 3.2.3.2 (page 177-181); Section 3.2.3.2.2 (page 181-182);	Conclusions NMP has been evaluated in several in vitro and in vivo genotoxicity assays that cover a range of endpoints, including chromosomal aberration, DNA damage and repair, and point mutations. Negative results in these mammalian and bacterial test systems representing multiple endpoints indicate that NMP is unlikely to be genotoxic. In a 2-year inhalation cancer bioassay, Sprague-Dawley rats (120 per sex per concentration) were exposed in a whole-body experiment to NMP vapor concentrations of 41 and 405 mg/m3 (0, 10 and 100 4153 ppm) for 6 h/day, 5 days/week. Survival of treated rats did not differ from controls. Other than an increase in pituitary adenocarcinomas at 41 mg/m3 at 18 months but not at 405 mg/m3 or at 24 months, there were no increases in incidence of benign or malignant tumors at any concentration (Lee et al., 4156 1987; DuPont, 1982). In an oral dietary study, NMP was examined for its chronic toxicity and carcinogenic potential in groups of 62 male and 62 female Sprague-Dawley rats at concentrations of 0, 1600, 5000 or 15000 ppm (about 66/88, 207/283, 678/939 mg/kg bw/day, males/females) in food for two years. The survival of female rats was not affected, but males in the high dose group had lower survival due to increased severe chronic-progressive nephropathy. The

Chemical	Draft RE Links & Sections	Weight of the Scientific Evidence for Cancer MOA
		incidence of benign or malignant tumors was not increased among rats (Malley et al., 2001; NMP Producers Group, 1997). NMP was also administered to groups of 50 male and 50 female B6C3F1 mice receiving dietary concentrations of 0, 600, 1200 and 7200 ppm (about 89/115, 173/221, 1089/1399 mg/kg-bw/day, males/females) in an 18-month study. There was no difference in survival of treated mice compared with controls. Among the 7200 ppm males, incidences of liver carcinomas were increased, whereas the incidence in females was within the historical control range. Increased incidences of liver adenomas were also noted at 7200 ppm; these occurred in both sexes. NMP also caused other substance-related effects in the liver at 1,200 and 7,200 ppm. For example, increased metabolic activity was observed. In addition, mice exhibited increased liver weights and incidences of foci of cellular alteration in the liver at 7200 ppm in both sexes. In the 1200 ppm group, increased liver weights were also observed among males and 3/50 of the mice exhibited centrilobular liver cell hypertrophy (Malley et al., 2001) and NMP Producers Group, 1999a, as cited in OECD (2007b). Results of cancer bioassays for NMP are summarized in Table 3-6.

*Indicates draft REs that have completed SACC peer review.